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INFORMATION PROCESSING AND COLLECTIVE BEHAVIOR IN A MODEL NEURONAL SYSTEM

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14. ABSTRACT

This project used neurons in the suprachiasmatic nucleus to understand information processing and collective behavior. The work is computational, and all work done with mathematical models that have been fit to experimental data. Models simulated up to 20,000 neurons in which internal molecular oscillations, with a period of around a day, are generated. On a fast neuronal timescale, these rhythms are co-ordinated and used to process environmental information. By studying this system, we learn about how multiagent systems can efficiently process environmental signals. Our progress was superb and lead to many key papers in high-impact journals. There was also great interest in our work, and we were called on to additionally explore how similar systems in other tissues (e.g. the heart) or organisms (e.g. the Monarch, which is currently being studied by other AFOSR researchers). This was done in addition to meeting the original goals of the grant.

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Grant Title: Information Processing and Collective Behavior in a Model Neuronal System

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Reporting Period: 7/15/2011-12/31/2013

Program Manager: Patrick Bradshaw

PI: Daniel Forger, University of Michigan

Table of Contents:

Overview: This project used neurons in the suprachiasmatic nucleus to understand information processing and collective behavior. The work is computational, and all work done with mathematical models that have been fit to experimental data. Models simulated up to 20,000 neurons in which internal molecular oscillations, with a period of around a day, are generated. On a fast neuronal timescale, these rhythms are co-ordinated and used to process environmental information. By studying this system, we learn about how multiagent systems can efficiently process environmental signals.

Our progress was superb and lead to many key papers in high-impact journals. There was also great interest in our work, and we were called on to additionally explore how similar systems in other tissues (e.g. the heart) or organisms (e.g. the Monarch, which is currently being studied by other AFOSR researchers). This was done in addition to meeting the original goals of the grant.

Quad Chart:

Information Processing and Collective Behavior in a Model Neuronal System, Forger PI

Objectives:

(1) Understand Signal Processing in the Core Daily Pacemaker within the Brain (SCN)

(2) Understand the unique electrical properties of SCN neurons

(3) Understand how neuronal systems use clocks to process information.

Technical Approach:

- Develop mathematical models for timekeeping within cells
- Develop methods to extract optimal schedules from models
- Close comparison with data and collaboration with experimentalists

Accomplishments:

- Developed detailed models of the molecular basis of of rhythm generation
- Developed an electrophysiological model for neuronal information processing in the core pacemaker
- Determined how the molecular clock controls the electrical activity of neurons and cardiac cells
- Determined schedules which decrease the time to overcome jetlag by 50% or more.

DoD Benefit:

- Significantly reduce jetlag and poor performance on night shifts and missions.
- Understand navigation using time cues and the Sun
- Understanding of information processing in an unexplored system of the brain.
- Understanding how oscillatory information is processed in noisy environments.
- Better control of timekeeping would lead to treatments for depression and methods to improve performance

Grant defunding due to the Sequester: Unfortunately, on June 18th 2014, less than one month before the halfway mark and the start of the 3rd fiscal year, we received an email from AFOSR that "Unfortunately the sequestration order canceling approximately $85 billion in budgetary resources has impacted your grant … and further funding for this effort is not available." This was very surprising to us since all indications to that point, from AFOSR and the academic community, had been that our progress was stellar. No indication was given that this action was taken because our grant was in any way deficient.

With much difficulty, much effort by the PI and much help from the University of Michigan, we were able to comply with this unusual grant action. We are also grateful to the AFOSR employees who helped us comply. The performance period was extended until the end of 2013, to use unspent funds to protect the research that had been done as much as possible, reorganize personnel and minimize waste. The work planned for years 3 and 4 were defunded (Aims 1.3 and 3) from the grant.

Special honors and indications of our progress: Our manuscript published, in Molecular Systems Biology, was highlighted by the faculty of 1000, a rare honor by arguably the leading scientific review board. We have also been invited to give several high profile talks on this work, including international conferences in Taiwan, Japan and China, as well a top conferences in the US, including two invited talks in Gordon Conferences. Dr. Forger also was promoted early to full Professor of Mathematics at the University of Michigan, and went through a rigorous review of his research, where the results of this project were highlighted. Our annual reports were approved without any concerns raised.

Broader Interactions with the Air Force: The Air Force took particular note of this work. In particular, we were invited to visit the 711th Human Performance Wing at Wright Patterson AFB to give a briefing on our work. We also presented our work at AFRL in Eglin AFB as part of a larger program review. Our work has been presented in each AFOSR spring review. Moreover, we were asked to provide support for an AFOSR project headed by Steve Reppert on Monarch Butterfly navigation. We visited the Reppert lab at the UMASS Medical School and have had many (at times weekly) telecoms with them and Eli Shlizerman at the University of Washington. In summary, we were happy to work with many groups within or funded by the Air Force. This unusual level of interaction shows how our work is directly relevant for the Air Force mission.

Publication and Dissemination of Results: A highlight of our grant is the number of papers we have published reporting results. While we received only two years of funding, we were still able to publish four papers, have a fifth in press and a sixth in the final stages of review. Even more impressive was the fact that these six papers are all at absolute top journals, journals that often publish work that takes years to develop. This indicates an unusual amount of productivity on our part.

Since the majority of our work is now, or will soon be publically available, we will simply summarize these results, and, as is standard for final reports, point the reader to the publications for details. We will describe in further depth work that we have performed which is not published.

Since the Air Force was particularly interested in the results of one paper on optimal schedule design for jet lag, we have built an iphone app, ENTRAIN, to distribute the results of our work. Since the closing of the grant, we have improved on this app to allow for models to be simulated on the iphone and give predictions about sleep drive and circadian phase. We have also tested the app in many conditions, and made it more user friendly. The app has been submitted to the itunes store for dissemination and free download. Once approval by apple, it will be released around the date of the publication of our manuscript in PLoS Computational Biology.

In summary, our work is now publically available, or will soon be. For this reason, we provide a summary of our results below, and point the reader to the full reports.

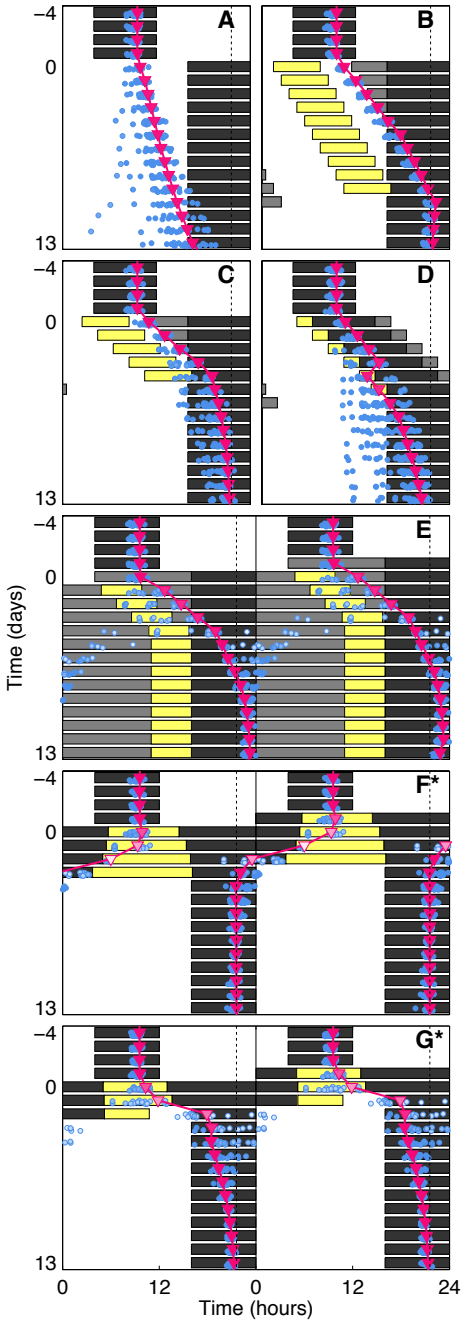
Summary of Serkh and Forger, "Optimal Schedules of Light Exposure for Rapidly Correcting Circadian Misalignment." Accepted in PLoS Computational Biology

Summary from paper: When our body's internal timekeeping system becomes misaligned with the time of day in the outside world, many negative effects can be felt, including decreased performance, improper sleep, and jet lag. When misalignment is prolonged, it can also lead to serious medical conditions, including cancer, cardiovascular disease, and possibly even late-onset diabetes. Rapid readjustment of our internal daily (circadian) clock by properly timed exposure to light, which is the strongest signal to our internal circadian clock, is therefore important to the large proportion of the population which suffers from misalignment, including transmeridian travelers, shift workers, and individuals with circadian disorders. Here we develop a methodology to determine schedules of light exposure which may shift the human circadian clock in the minimum time. By calculating thousands of schedules, we show how the human circadian pacemaker is predicted to be capable of shifting much more rapidly than previously thought, simply by adjusting the timing of the beginning and end of each day. Schedules are summarized into general principles of optimal shifting, which are supported by general mathematical arguments.

Role in aims of grant: This work was not highlighted in the original grant, but was encouraged by Program Managers Willard Larkin and Patrick Bradshaw and received much additional internal funding from the University of Michigan. It was mentioned in

the spring review, and was the subject of the requested briefing at the 711th Human Performance Wing. It is a natural extension of the original aims of the grant, as the suprachiasmatic nucleus, the focus of the grant, has its major role to control daily timekeeping.

Figure from paper:



Legend: Comparison of schedules for a 12-hour shift of the light-dark cycle.

Predicted circadian phase, indicated by simulated core body temperature minima (CBTmin, magenta triangles), is plotted against the pattern of exposure to bright light (10,000 lux, yellow), moderate light (100 lux, white), dim light (5 lux, gray), and darkness (0 lux, black). Predicted CBTmin under noisy light levels (See supplemental figure S1), with circadian period randomly sampled from an experimentally measured distribution, is plotted for 20 hypothetical subjects (blue circles). Circadian amplitude at CBTmin is indicated by the brightness of the markers, with white corresponding to zero amplitude. The timing of entrained CBTmin in the new time zone is indicated by the dotted line. The subjects are initially entrained to a 16:8 LD-cycle in moderate light. At day 0 the schedule shift occurs. The six schedules are compared are: (**A**) The abruptly shifted LD-cycle; also called a slam shift. (**B**) Times of light exposure and avoidance in the new time zone are prescribed to quicken re-entrainment. Phase delays of 1 hour/day are assumed. Based on the recommendations proposed by R. Sack.(**C**) Times of light exposure and avoidance are prescribed, with an assumed phase delay of 2 hours/day. Based on the recommendations proposed by J. Waterhouse et.al. (**D**) The sleep/dark region is gradually delayed, with 2 hours of bright light before bed and 2 hours of light avoidance after wake. Assumed delay of 2 hours/day. Based on the recommendations proposed by C. Eastman et.al. (**E**) A PRC is used to place a series of 5 hour light stimuli, in a background of dim light, in order to produce a large delay. The timings are refined using a model proposed by D. Dean et.al. (**F**) Our optimal schedule for complete re-entrainment in minimum time. A model is used to compute the mathematically optimal schedule of light exposure, which resets the model in the least possible amount of time.

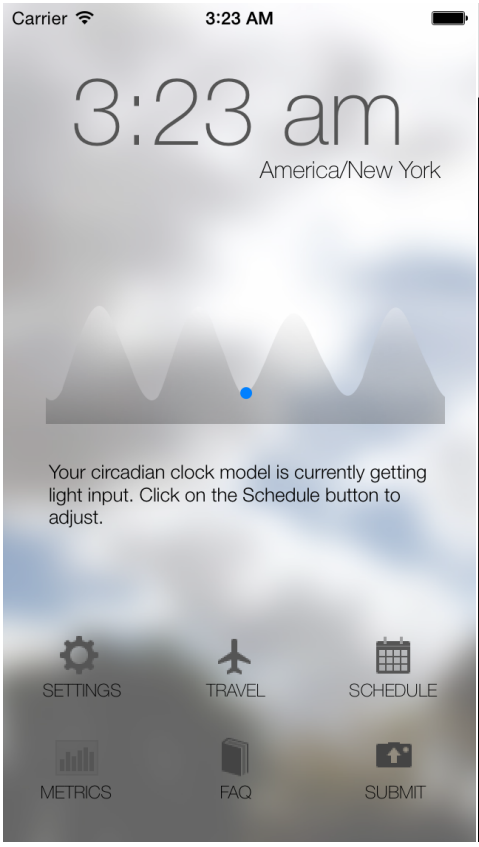
(**G**) Our optimal schedule for partial re-entrainment in minimum time, designed to place CBTmin at the beginning of the sleep/dark region as quickly as possible.

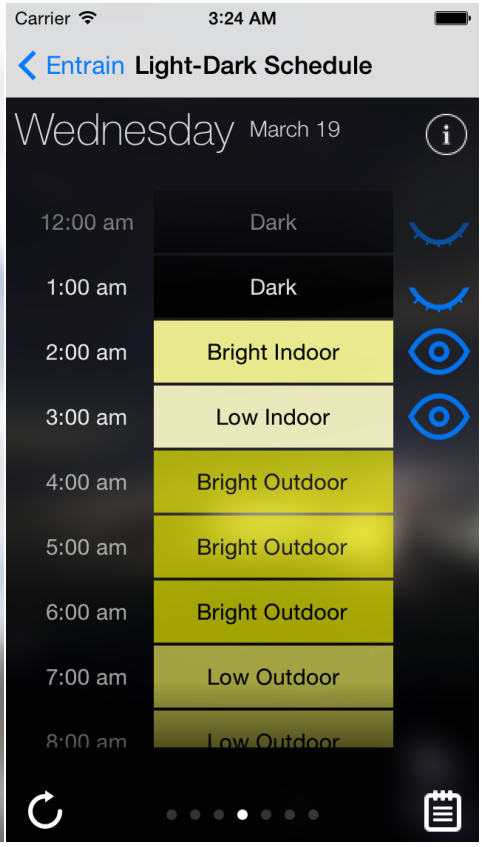
Summary of ENTRAIN app

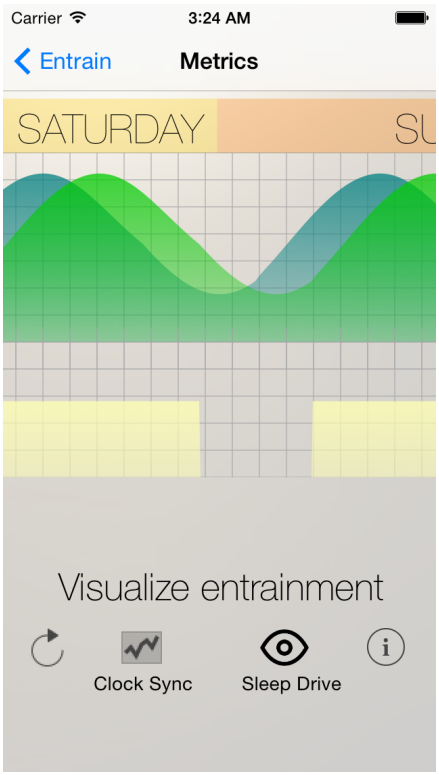
Summary: We have developed an iphone app for which users enter in their lighting and sleep-wake history as well as goals for shifting schedules or changing timezones. The app then displays the optimal schedules to get the user to the new timezone or schedule. We predict that the app can reduce the amount of time needed to adjust to a new timezone by half or more. The app also simulates models on the iphone and presents the user with their predicted circadian phase (how aligned the are with the current timezone) as well as sleep drive (i.e. how tired they are). Much work went into making the app user friendly. Users will also be able to report their schedules to our servers allowing us to conduct in the future the potentially largest scale study of human circadian alignment and jetlag ever performed. The app has been submitted to the itunes store for release as a free app.

Role in aims of grant: This app was designed to make the results of the manuscript by Serkh and Forger publically available. AFOSR funds were used to integrate the schedules from Serkh and Forger into the app. University of Michigan funds were used to create the broader app, include model simulations on the app, fix bugs, make the app user friendly and make the app acceptable for release.

Screen Shots:





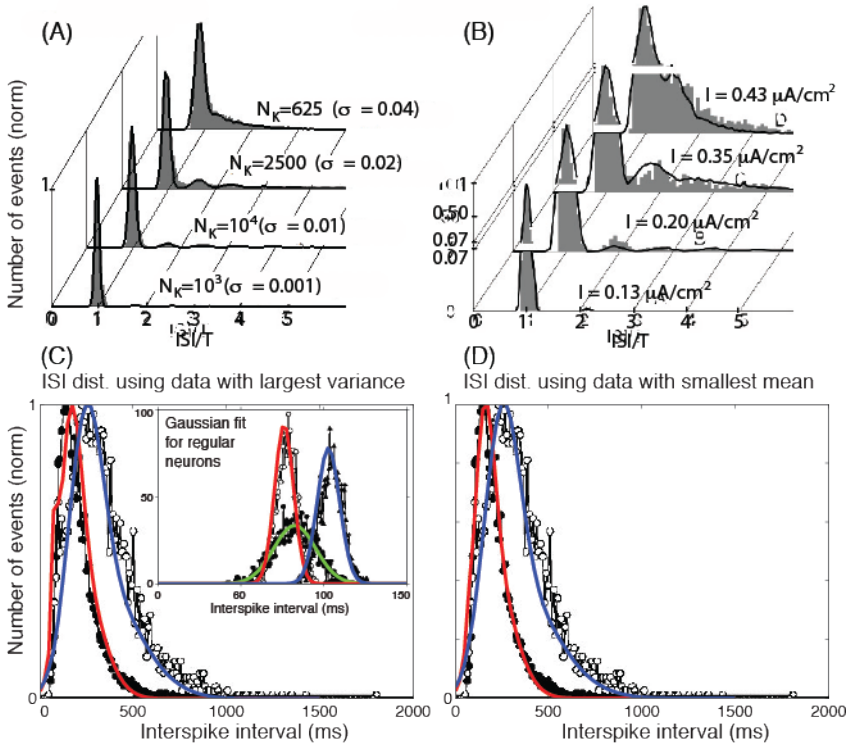


Summary of Bodova, Paydarfar and Forger, "Characterizing spiking and quiescence in spiking Type II neurons" in revision, Journal of the Royal Society Interface

Summary from paper: Stochastic channel dynamics and noisy neuronal inputs can have a large influence on the behavior of a neuron. To understand, compare and contrast the role of noise coming from various sources, i.e., potassium channels, sodium channels, input signal, we simulate the classical Hodgkin-Huxley (HH) model with stochastic channel dynamics and deterministic stimuli using the kinetic Monte Carlo and Langevin stochastic techniques and explore how the mean firing rate and other signal properties depend on the constant input current and the number of sodium or potassium channels in the neuron. We compare these results with experiments on a giant squid axon with variable inputs that show low channel variability. We find that the type and magnitude of noise acts the neuronal properties (mean firing rate, inter-spike interval distribution) significantly. However, these patterns may be accurately described, independently of the source of noise, by a simple probabilistic model that captures the dynamical features of the HH model and where the type of noise only enters into the model parameters.
This simple model we developed, which is amenable to mathematical analysis, matches both our numerical simulations with channel noise and experiments with input current noise in terms of the distribution of inter-spike interval and distribution of burst length. Thus, we show how the complex effects of noise can be understood through a simple yet general probabilistic model.

Role in aims of grant: A major part of aims 1 and 2 of the grant is to understand the electrical activity of suprachiasmatic nucleus neurons. This paper presents a simple way to characterize their behavior. We extend this analysis to a broad class of neurons to make it broadly applicable.

Figure from paper:



Legend: Fitting the SQ model to numerical and experimental data. (A) Simulation of the ISI distribution by the LS method (gray histograms) versus the SQ model (black lines) for sodium channel with 2500 channels and an applied current (I) of 8. (B) Experimental recordings of the giant squid axon from (gray histograms) with the SQ model distribution (black lines). These plots show the accuracy of the SQ model in representing the simulations and experimental data. All data was normalized with respect to the deterministic oscillations period **T** (that is approximately 11.8, 11.2, 12.4, 11.7 for cases **I** = 0**:**13, **I** = 0**:**20, **I** = 0**:**35, **I** = 0**:**43 **u**A/cm2) therefore the first peak is centered around

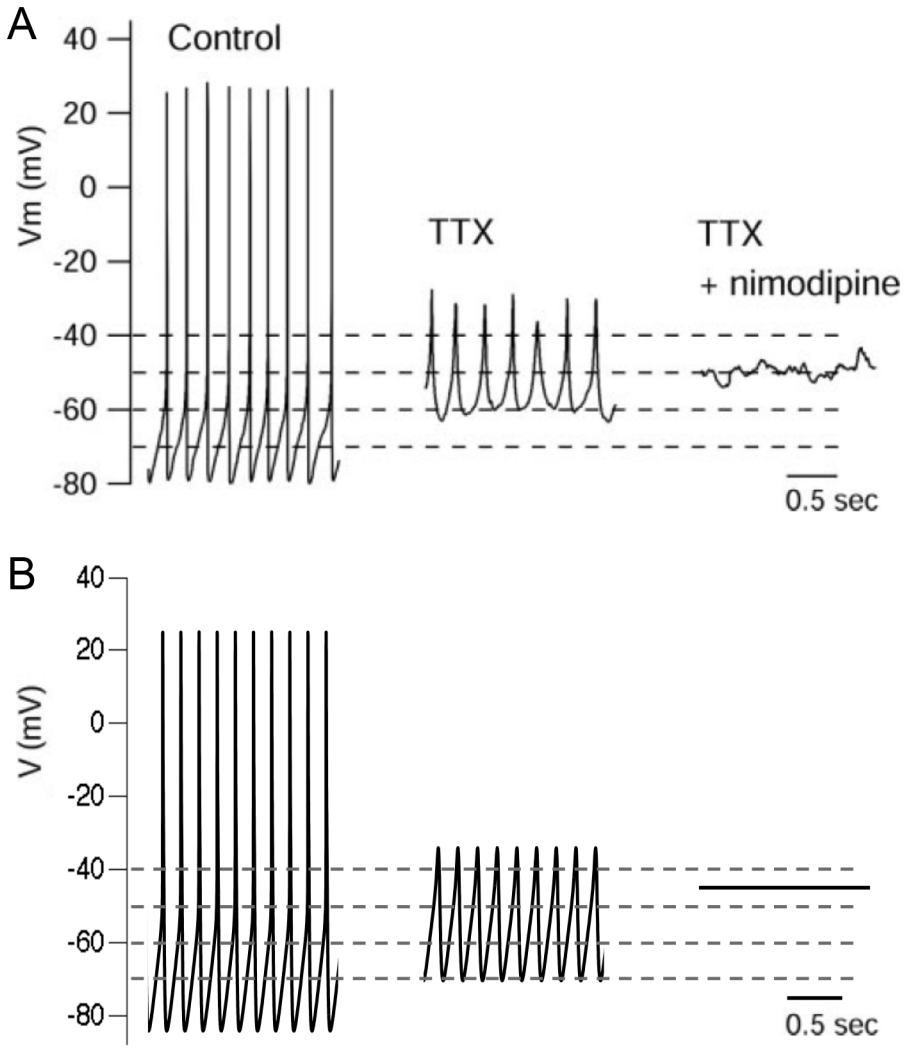
one. (C), (D) Fitted ISI histograms from suprachiasmatic nucleus neurons that correspond to regular firing neurons in the upper right corner of (C) are fitted to a Gaussian distribution. These are used in the SQ model to fit the ISI distribution of the irregularly spiking neurons on (C) and (D).

Summary of Diekman, Belle, Irwin, Allen, Piggins and Forger, Causes and consequences of hyperexcitation in central clock neurons PloS Computational Biology 2013 9:e1003196

Summary from paper: Hyperexcited states, including depolarization block and depolarized low amplitude membrane oscillations (DLAMOs), have been observed in neurons of the suprachiasmatic nuclei (SCN), the site of the central mammalian circadian (~24-hour) clock. The causes and consequences of this hyperexcitation have not yet been determined. Here, we explore how individual ionic currents contribute to these hyperexcited states, and how hyperexcitation can then influence molecular circadian timekeeping within SCN neurons. We developed a mathematical model of the electrical activity of SCN neurons, and experimentally verified its prediction that DLAMOs depend on post-synaptic L-type calcium current. The model predicts that hyperexcited states cause high intracellular calcium concentrations, which could trigger transcription of clock genes. The model also predicts that circadian control of certain ionic currents can induce hyperexcited states. Putting it all together into an integrative model, we show how membrane potential and calcium concentration provide a fast feedback that can enhance rhythmicity of the intracellular circadian clock. This work puts forward a novel role for electrical activity in circadian timekeeping, and suggests that hyperexcited states provide a general mechanism for linking membrane electrical dynamics to transcription activation in the nucleus.

Role in aims of the grant: This paper reports our finding from Aim 2 of the grant. As can be seen from the paper, the work went very much as expected. This paper also reports a better ionic mathematical model of the electrical activity of suprachiasmatic nucleus neurons, which helps in a better approach to aims 1.1 and 1.2.

Figure from paper:



Legend: Model simulations of SCN AP firing and nimodipine-sensitive membrane oscillations in the presence of TTX match published experimental data.

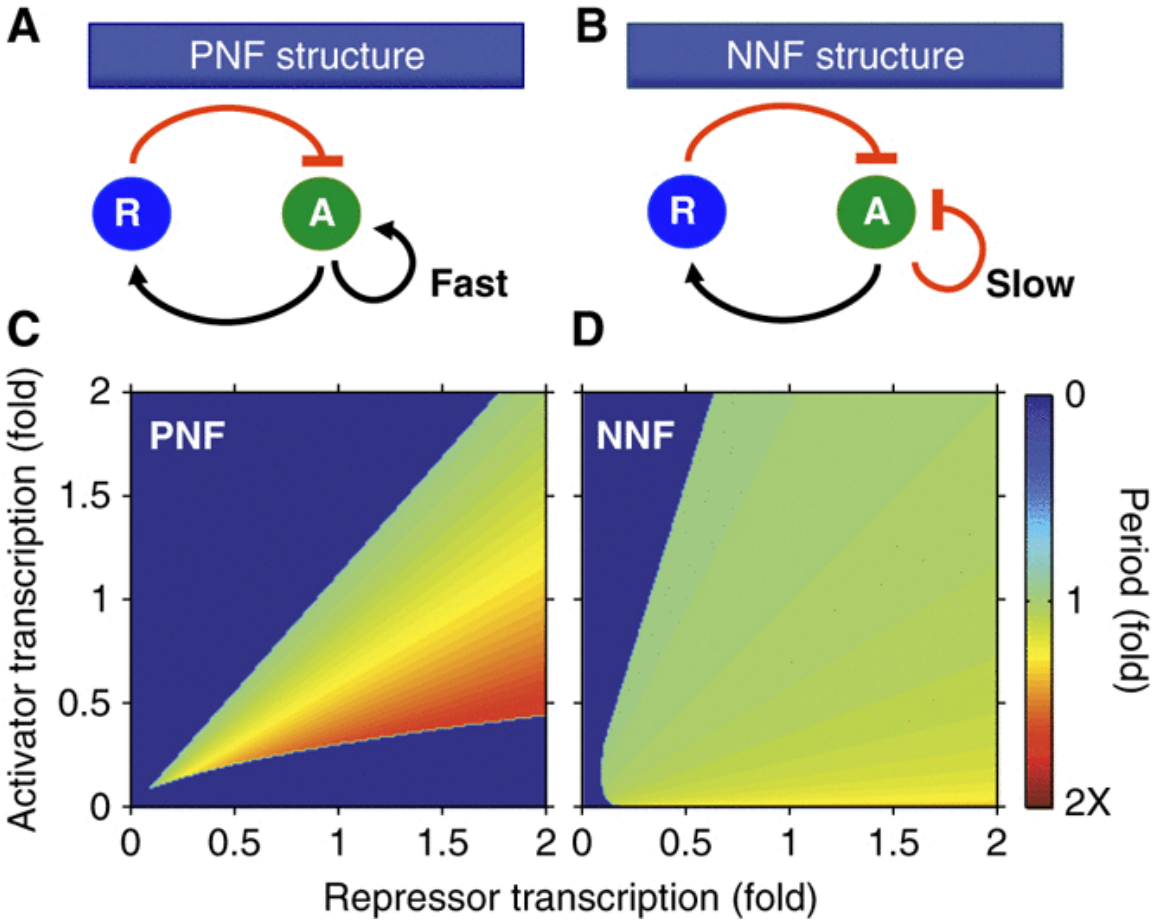
Reproduction of experimental data from suprachiasmatic nucleus neurons showing the effect of cumulative application of 300 nM TTX and 1 μM nimodipine, blocking calcium

channels on a spontaneously firing SCN neuron. The membrane potential oscillations in the presence of TTX (TTXLAMOs) are silenced by nimodipine. **B**. Model exhibiting spontaneous AP firing (g_{Na} = 229 nS, g_{CaL} = 6 nS) and membrane potential oscillations in the presence of simulated TTX (g_{Na} = 0). The oscillations are silenced by simulated nimodipine application (g_{CaL} = 0).

Summary of Kim and Forger "A mechanism for robust circadian timekeeping via stoichiometric balance." Molecular Systems Biology 2012 8:630

Summary from paper: Circadian (~24 h) timekeeping is essential for the lives of many organisms. To understand the biochemical mechanisms of this timekeeping, we have developed a detailed mathematical model of the mammalian circadian clock. Our model can accurately predict diverse experimental data including the phenotypes of mutations or knockdown of clock genes as well as the time courses and relative expression of clock transcripts and proteins. Using this model, we show how a universal motif of circadian timekeeping, where repressors tightly bind activators rather than directly binding to DNA, can generate oscillations when activators and repressors are in stoichiometric balance. Furthermore, we find that an additional slow negative feedback loop preserves this stoichiometric balance and maintains timekeeping with a fixed period. The role of this mechanism in generating robust rhythms is validated by analysis of a simple and general model and a previous model of the Drosophila circadian clock. We propose a double-negative feedback loop design for biological clocks whose period needs to be tightly regulated even with large changes in gene dosage.

Role in aims of the grant: This work presents a mathematical model which explains what drives neuronal hyperexcitation, as described in aims 1.1 and 1.2, as well as gives a better description of the molecular timekeeping which controls calcium in aim 2.



Legend: **A design suitable for cellular clocks with a fixed period.** (**A**) A single-negative feedback loop with an additional fast positive feedback loop, with which activator (*A*) activates itself and degrades quickly. This structure has been identified in various biological oscillators like the cell cycle and pacemaker in the sino-atrial node. (**B**) A single-negative feedback loop with an additional slow negative feedback loop, with which activator (*A*) represses itself and degrades slowly. Circadian clocks in mammals or *Drosophila* have been shown to have this structure(**C**, **D**) The period of the NNF is nearly constant for the perturbations in transcription rates while the period of the PNF changes about two-fold. The period is plotted as a color where green refers to the period with the unperturbed parameters.

Summary of Kim and Forger, "On the Existence and Uniqueness of Biological Clock Models Matching Experimental Data" Society for Industrial and Applied Mathematics (SIAM) Journal on Applied Mathematics, 2012 72:1842

Summary from paper: The development of luciferase markers and other experimental techniques has allowed measurement of the timecourses of the expression of genes and proteins with remarkable accuracy. Since these data have been used to develop many mathematical models, it is important to ask whether this problem of model building is well-posed. Here, we focus on a common form of ordinary differential equation (ODE) models for biological clocks, which consist of production and degradation terms, and assume we have an accurate measurement of their solution. Given these solutions, do ODE models exist? If they exist, are they unique? We show that timecourse data can sometimes, but not always, determine the unique quantitative relationships (i.e., biochemical rates) of network species. In other cases, our techniques can rule out functional relationships between network components and show how timecourses can reveal the underlying network structure. We also show that another class of models is guaranteed to have existence and uniqueness, although its biological application is less clear. Our work shows how the mathematical analysis of the process of model building is an important part of the study of mathematical models of biological clocks.

Role in aims of grant: A major them of the grant is information processing. Here, we study how information is processed in biochemical networks. We also show how data can be used to fit models, which is needed for all parts of the grant. It also shows how we can determine the structure of an unknown system based on rhythmic measurements of its components. Understanding a system based on rhythmic measurements is an important problem for our military.

Figure from paper:

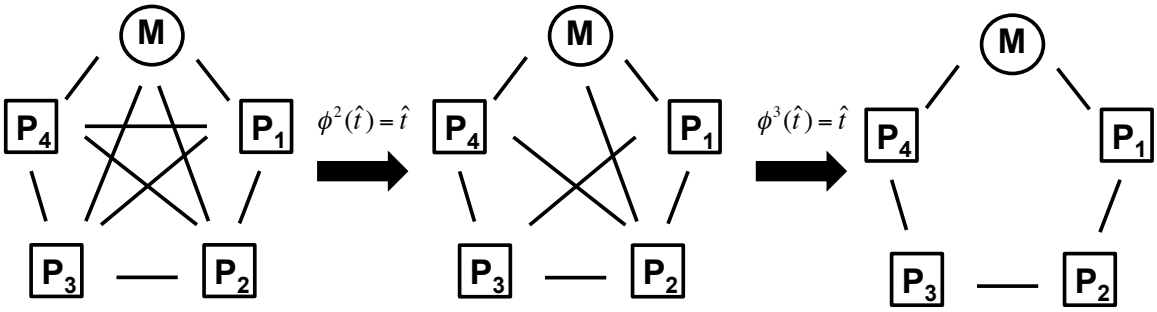


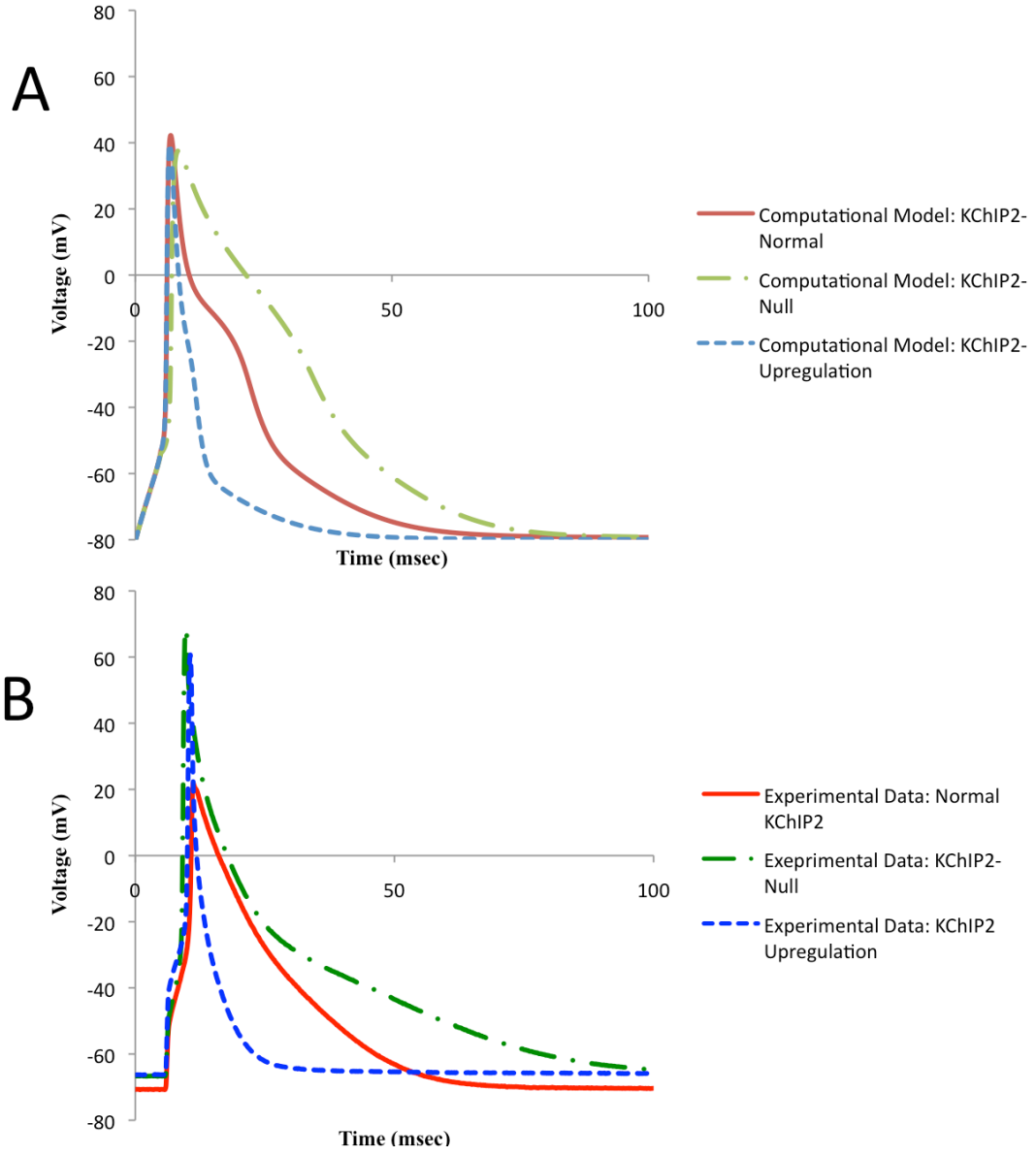
Figure Legend: We consider a system with five components, whose interactions form a ring (i.e. P_1 affects P_2 which affects P_3 …). The output of the system is calculated (measurements), and the interactions are forgotten. Based on measurements of the components, we show how to rule out possible interactions. All possible interactions are shown on the left, and after two iterations of method, we determine all unknown interactions. This shows how the structure of a system can be determined based on rhythmic measurements.

Summary of Fotiadis and Forger, "Modeling the effects of the circadian clock on cardiac electrophysiology" Journal of Biological Rhythms 2013 28:69

Summary from paper: An internal circadian clock regulates the electrical activity of cardiac myocytes controlling the expression of potassium channel interacting protein-2 (KChIP2), which is a key regulator of cardiac electrical activity. Here, we examine how the circadian rhythm of KChIP2 expression affects the dynamics of human and murine ventricular action potentials (APs), as well as the intervals in the equivalent electrocardiograms (ECGs) reflecting the duration of depolarization and repolarization phases of the cardiac ventricular APs (QRS and QT intervals), with mathematical modeling. We show how the internal circadian clock can control the shape of APs and, in particular, predict AP, QRS, and QT interval prolongation following KChIP2 downregulation, as well as shortening of AP, QRS, and QT interval duration following KChIP2 upregulation. Based on the circadian expression of KChIP2, we can accurately predict the circadian rhythm in cardiac electrical activity and suggest the transient outward potassium currents as the key current for circadian rhythmicity. Our modeling work predicts a smaller effect of KChIP2 on AP and QT interval dynamics in humans. Taken together, these results support the role of KChIP2 as the key regulator of circadian rhythms in the electrical activity of the heart; we provide computational models that can be used to explore circadian rhythms in cardiac electrophysiology and susceptibility to arrhythmia.

Role in aims of grant: Aim 1 studies how an internal molecular clock can induce excited states in neurons. We noticed that similar behavior is also seen in cardiac cell and control heart rate (which is of interest to the military). We thus applied work in Aim 1 not only to neurons in the suprachiasmatic nucleus, but also cardiac cells, and predicted how a clock can excite these cells, and control heart rate.

Figure from paper:



Legend: Action Potentials (APs) based on our murine computational model and compared with experimental data by Jeyaraj et al. (2012). (A) APs predicted by our model in response to relatively normal concentrations, downregulation, and upregulation of KChIP2, a key circadian regulator of cardiac electrophysiology. (B) APs corresponding to relatively normal concentrations, absence, and upregulation of KChIP2 from the experimental data published by Jeyaraj et al. (2012)